REMARKS/ARGUMENTS

Claim 1 is active in this case. Claim 1 has been amended for clarity. Support is found in original Claim 1 and the specification as originally filed.

No new matter is believed to have been added by these amendments.

As discussed in the specification, e.g., on page 21 last paragraph, the claimed method for examining the caries risk finds unique applicability in that one can examine caries risk irrespective of the age and the salivary quantity as compared with a conventional immunity method by assessing the correlation between antibody titers directed to a specific peptide (SEQ ID NO:1) and using this antibody titer correlation to assess the risk of caries in an individual based on a DRB*1 HLA class II genotype. This method provides are more accurate testing method thereby having great value in the field of dental medicine. Moreover, this method has particular advantages for assessing caries risk in infants, less than about 6 years of age, due to their incomplete immune system and for which traditional immunological methods would not sufficiently detect the caries risk (see page 5, last paragraph of the specification).

Based on the fact that the enablement and obviousness rejections were maintained in the Official Action, it would appear that there are some fundamental misunderstandings about the claimed method. First it should be appreciated that in a single individual (or patient as in claim 1), he/she will have one genotype at a locus or two genotypes at a particular locus (here that locus is the DRB*1) due to the diploidy of a human's genome. Thus, a patient is either homozygous or heterozygous at that locus. This is very common knowledge in the field.

For example, referring to the Table on page 21 of the specification, a patient can have a genotype of (1) DRB1* 0803/DRB*1-803 or (2) DRB1*-403DRB1*1406.

The invention (and claim 1 as presented) requires that a table be prepared before the method. This table correlates homozygous (same genotype on each allele) or heterozygous

(different genotypes on each allele) genotypes at the DRB*1 and the relationship of an antibody titer of a secretory IgA in human saliva against an antigen (defined by SEQ ID NO:2 in claim 1). For example as shown in the table in the previously submitted Rule 132 Declaration, when a patient is heterozygous at DRB1* and only one genotype had been identified before (e.g., DRB1* 0803), the caries risk of the patient could not be determined because if another allele was DRB1*0410, the caries risk was low, and if it was DRB*1 1202, the caries risk is high. After determining what combination the patient had, in terms of genotypes, the caries risk can be determined by comparing that genotype to the table.

Therefore, the inventors have shown that it is possible to examine caries risk in a patient through the use of genotyping analysis. Tthe method defined in the claims (1) can be practiced by one of skill without undue experimentation and (2) would not have been obvious in view of the cited publications.

The Examiner has maintained the rejection in view of Acton, Matsushita and Senpuku on the basis that it would have been obvious to select any peptide within the region of highly immunogenic epitopes including SEQ ID NO:1.

Acton et al. describes a correlation between HLA-DRB1 genotype and *S. mutans* levels evaluated in representative subjects (see pp. 986). In Acton, there is simply a correlation between levels of bacteria and genes; no relationship of assessed DRB genotypes to caries risk is described and moreover, large number s of oral bacteria do not necessary correlate to high caries risk. Therefore, it is respectfully submitted that a primary basis for this rejection (that Acton "teaches determining caries risk based on HLA genotype"; page 16, last paragraph of the Official Action) is incorrect.

Matsushita et al. describes multiple antigenic epitopes identified within the full-length of PAc (FIGS. 3-5) by reacting synthetic peptides of PAc with serum and saliva samples

removed from some subjects. In the last paragraph of the discussion (page 4040, second column), Matsushita simply suggest the potential for using the epitopes for developing a diagnositic test or a vaccine. Nothing in this publication provides any indication that one could correlate DRB1 genotypes with caries risk and specifically that the peptide as defined in claim 1 would be beneficial for this purpose.

Senpuku et al. describes several HLA-DR-binding motifs/regions identified in PAc. As discussed throughout the article and, for example in the Abstract, these peptides were identified and were believed to be relevant for providing a therapy for treating dental caries. This cannot be a basis to allege that specifically using SEQ ID NO:1 to identify correlation between genotype and antibody titer could successfully be used to examiner caries risk. Nothing in this article would lead one to understand a correlation between DRB1 genotypes and caries risk.

On the basis of the above-discussion, it is requested that the rejection under 35 USC 103 be withdrawn.

In the Official Action, the Examiner has maintained that the claimed method is not enabled. In particular, the Examiner states that the HLA-DRB1 gene is highly polymorphic (page 5 of the Official Action), to determine the association of genotype and carries risk a statistically significant data set is required (pages 7-8 of the Official Action), not every DRB-1 gene will be predictive because "determining an association requires finding a particular allele multiple times in affected or control subjects, and it is a preponderance of alleles in a particular group, not just a single instance of an allele and a single subject, which serves as the basis of the determination." (page 8 of the Official Action). According to the Examiner, as the specification does not identify any DRB-1 carries or relationship of statistical significance, the claims are not enabled. In addition, the Examiner refers to the table in the

Declaration as evidence of the unpredictability of the claimed method (see page 15 of the Official Action).

It is respectfully submitted that there is a fundamental misunderstanding about the invention and what is required to practice the invention.

The invention (and claim 1 as presented) requires that a table be prepared before the method. This table correlates homozygous (same genotype on each allele) or heterozygous (different genotypes on each allele) genotypes at the DRB*1 and the relationship of an antibody titer of a secretory IgA in human saliva against an antigen (defined by SEQ ID NO:2 in claim 1). For example as shown in the table in the previously submitted Rule 132 Declaration, when a patient is heterozygous at DRB1* and only one genotype had been identified before (e.g., DRB1* 0803), the caries risk of the patient could not be determined because if another allele was DRB1*0410, the caries risk was low, and if it was DRB*1 1202, the caries risk is high. After determining what combination the patient had, in terms of genotypes, the caries risk can be determined by comparing that genotype to the table.

Therefore, the inventors have shown that it is possible to examine caries risk in a patient through the use of genotyping analysis by comparing that genotype to a table that correlates genotypes to caries risk (determined by antibody titer).

Genotyping is a procedure that is common and well-used in the field.

Determining antibody titer is common and well-used in the field.

What the inventors have shown is that when you correlate these parameters in a table one can then assess a patient's genotype, compare it to the table, and from this examine the caries risk in that patient, simply, accurately, and in many patients who would otherwise be unable to be examined. That is, when a patient's genotype(s) of a DRB*1 has been identified,

the patient's caries risk can be easily examined by looking at the caries risk at the point of intersection in a table as, for example, shown in the Rule 132 Declaration previously made of record in this case. That caries risk and alleles (or genotype combinations) are statistically related and can be used to assess caries risk is shown by the description in the specification and the Rule 132 Declaration mentioned.

Therefore, as the tools for performing the method, generating the table (prepared beforehand) and making the requisite comparisons is within the skill in this field, it is respectfully submitted that it would not require undue experimentation for such a person to carry out the claimed method based on what is described in the specification as originally filed.

Accordingly, withdrawal of this ground of rejection is requested.

The rejection under 35 USC 112, second paragraph is believed to be addressed by the amendments.

Claim 1 has been amended to incorporate Claim 2 and therefore any criticisms of original Claim 1 should no longer be applicable as the steps used for determining caries risk have been set forth in the body of Claim 1.

As for how to identify a genotype, it should now be clear that the genotype is identified from a subject and obtaining a genetic sample and determining its sequence or otherwise is well within the skill in this field, e.g. using PCR (see also the specification on pages 13-17).

As to what is meant by "identified beforehand," it should now be clear that the genotypes correlating to caries risk is determined prior to carrying out the claimed method and the correlation between genotype and caries risk is drawn from this relationship where

the caries risk is assessed by the antibody titer. For further guidance on this point see the discussion on pages 20-21 of the specification culminating in Table 1 on page 20.

Withdrawal of this ground of rejection is requested.

Applicants also request a Notice of Allowance.

Respectfully submitted,

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